BRIEFING DOCUMENT

NDA # 21-239
Sponsor: Genelabs Technologies Inc.
Drug: Dehydroepiandrosterone [GL-701, prasterone]
Indication: Systemic Lupus Erythematosis

SUMMARY OF THE PHARMACOLOGY/TOXICOLOGY REVIEW OF PRASTERONE

Dehydroepiandrosterone [DHEA] is an endogenous substance that is the precursor to both estrogenic and androgenic hormones, including androstenedione, androstenediol, testosterone, estrogen, estradiol, and dihydrotestosterone. It is the major steroid secreted from the adrenal in humans and some other nonhuman primates, but the serum levels of this steroid are considerably lower in other mammals. The literature suggests that some of the effects of DHEA are mediated, at least in part, by DHEA, but it is generally accepted that the biological activity of DHEA is primarily mediated by the androgenic and estrogenic metabolites. The literature also suggests that the potency of DHEA is generally less than its androgenic and estrogenic metabolites. DHEA has been shown to exert pleiotropic effects in nonclinical studies including effects on the immune system, the cardiovascular system, the central nervous system, and metabolism [e.g. bone, glucose, anti-obesity, and lipid].

The metabolism of DHEA is very complex and is further complicated by the existence of a number of factors that appear to impact the metabolism of DHEA including species, strain, gender, age, hormonal status [e.g. intact vs. ovariectomized or castrated], body composition, route of administration, and the steroidogenic or steroid metabolizing enzyme make-up of a given tissue. There do appear to be differences between humans and a number of animal species in the metabolism of DHEA based on serum concentrations of the various androgenic and estrogenic metabolites. However, serum levels may not be reflective of the metabolism in the peripheral tissues.[1] Due to the peripheral metabolism of DHEA, assessment of secondary endpoints in nonclinical studies, such as effects on reproductive organs, bone density, skin, obesity, and insulin sensitivity; reversal of the effects of gonadectomy on the prostate or uterus; and activity in models of autoimmunity, have been used as indirect indicators of whether metabolism is predominantly androgenic or estrogenic in a given species or animal model. In rodents both estrogenic and androgenic effects have been observed following DHEA administration, depending, in part, on the endpoint evaluated.

The Sponsor did not conduct any studies to demonstrate the efficacy of DHEA in SLE animal models. However, they did provide reprints of several articles indicating that when DHEA was administered to "SLE" mice and dosing was begun prior to the onset of clinical signs, there was improvement in a number of endpoints including survival. The Sponsor, however, did not provide any citations that indicated efficacy if DHEA was begun in these lupus models subsequent to the onset of signs. There is a report that indicated that if the sulfated form of DHEA [DHEAS] was administered to "SLE" mice subsequent to the development of clinical signs, neither serum dsDNA antibody titers were decreased nor survival prolonged. This led the authors to conclude that "DHEAS therapy used under similar conditions would not provide a clinically beneficial effect in the specific symptoms of immune complex-mediated glomerulonephritis".[2]

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[1] Labrie F et. al. [1997]. Physiological changes in dehydroepiandrosterone are not reflected by serum levels of active androgens and estrogens but of their metabolites: Intracrinology. *J Clin Endocrinol Metab*. **82:**2403-9

[2] Norton, SD et. al. [1997] Administration of dehydroepiandrosterone sulfate retards onset but not progression of autoimmune disease in NZB/W mice. *Autoimmunity* **26**(3):161-171.

Following several discussions with the FDA, the Sponsor agreed to conduct the following nonclinical studies: [1] a 6-month repeat dose study in dogs; [2] a full battery of reproductive toxicity studies; and [3] a full battery of genotoxicity assays. As a standard part of the review process, two pivotal nonclinical studies were audited by the FDA. This audit identified significant deviations from Good Laboratory Practices [GLP] in both studies. The file is still open and the Sponsor will have the opportunity to address these deficiencies.

The primary target organs in dogs administered DHEA were the reproductive organs, adrenal glands, and potentially the liver. The following toxicities were observed: [1] testicular hypospermatogenesis and epididymal oligospermia; [2] depletion of corpora lutea and 3^{o} follicles and cystic 3^{o} follicles; [3] mammary gland hypoplasia/atrophy; [4] lipid depletion of the adrenal zona reticularis; [5] decreased plasma cholesterol; and [6] increased serum ALT. The effects on the reproductive organs were not completely reversed after a 4-week recovery period

As anticipated, there were a number of reproductive disturbances observed in the rats. The changes included abnormal estrous cyclicity and a decrease in embryofetal viability following in utero exposure. There was no evidence of effects on male fertility in rats but the maximum dose used was inadequate. The data indicated delayed maturation [e.g. delayed ossification] and several abnormalities in external and skeletal observations including an increase in the incidence of bent ribs. Virilization, which has been reported in rats[3] and mice[4] following DHEA administration, was not observed in the studies conducted by the Sponsor, which may be a function of dose. There was no clearly defined developmental toxicity in the rabbits. There was no apparent treatment-related effect on a developmental battery, functional observational battery or reproductive outcomes in rats following in utero exposure to DHEA. However, fetal weights in both sexes of pups were decreased through the preweaning period and there was a trend toward reduced pup survival during the first postnatal week.

Under the conditions tested, DHEA was neither mutagenic in the bacterial reverse mutation assay nor clastogenic in the mouse micronucleus assay, but was clastogenic in Chinese hamster ovary [CHO] cells with and without metabolic activitation. Estrogens have also been found to be clastogenic.[5,6]

No studies were conducted by the Sponsor to address the potential carcinogenicity of DHEA as a result of an agreement between the Division and the Sponsor. This decision was based on the following considerations: [1] differences between humans and rodents in basal serum concentrations of DHEA/DHEAS; [2] apparent differences in metabolism between humans and rodents based on serum concentrations of the various metabolites of DHEA; [3] uncertainties regarding comparability of peripheral metabolism of DHEA between rodents and humans especially since serum levels of the metabolites may not accurately reflect metabolism within a given end organ; [4] metabolism of DHEA to both estrogenic and androgenic sex steroids and a knowledge of the effects of estrogens and androgens, including carcinogenic potential, in humans; and [5] potential risk:benefit considerations [e.g. efficacy of DHEA in treating a serious disease]. Based on these considerations, it was originally considered reasonable to label DHEA similarly to estrogens and androgens.

The literature indicates that DHEA has carcinogenic as well as chemoprotective potential in a number of animal models. The apparent contradiction is probably due, in part, to [1] the tumor type evaluated [e.g. hormone-responsiveness]; [2] whether the tumor was chemically induced; [3] the chemical used for induction; [4] the hormonal status of the animal [e.g. intact or neutered]; [5]

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[3] Goldman AS [1970]. Virilization of the external genitalia of the female rat fetus by dehydroepiandrosterone. *Endocrinol* **87**:432-435.

[4] Gandelman R, Simon NG, and McDermott NJ [1979]. Prenatal exposure to testosterone and its precursors influence morphology and later behavioral responsiveness to testosterone of female mice. *Physiol Behav* **23**(1):23-26.

[5] Hundal BA, Dillon VS, and Sidhu IS [1997]. Genotoxic potential of estrogens *Mutation Res* **389**:173-81.

[6] Marselos M and Tomatis L [1992] DES: II. Pharmacology, toxicology, and carcinogenesis in experimental animals. *Eur J Cancer* **29A**149-55.

timing, route of administration, and dose of DHEA; [6] the tissue evaluated; and [5] differences in species and strain. DHEA can be both stimulatory and inhibitory to hormonally responsive tumors. In rats, DHEA is a hepatocarcinogen secondary to peroxisomal proliferation.[7,8] Therefore, the relevance to humans is questionable. However, DHEA induced the development of hepatocellular carcinoma in rainbow trout and the development of this tumor was not associated with peroxisomal proliferation.[9]

CONCLUSIONS: As anticipated, DHEA exhibited hormonal effects on reproductive organs and reproductive function in dogs and rats. Other treatment-related effects in the dog included a decrease in serum cholesterol, lipid depletion of the zona reticularis, and an elevation in hepatic enzymes. Although the literature indicates that DHEA is generally less potent than its androgenic and estrogenic metabolites, the carcinogenic potential and the potential reproductive toxicity of DHEA is of concern.

Susan D. Wilson
Reviewing Pharmacologist/Toxicologist
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[7] Rao MS et. al. [1992]. Phenotypic properties of liver tumors induced by dehydroepiandrosterone in F-344 rats. *Jpn J Cancer Res* **83**(11):1179-83.
[8] Yamada J et. al. [1991]. Characteristics of dehydroepiandrosterone as a peroxisome proliferator. *Biochim Biophys Acta* **1092**(2):223-43.
[9] Orner GA et. al. [1995]. Dehydroepiandrosterone is a complete hepatocarcinogen and potent tumor promoter in the absence of peroxisome proliferation in rainbow trout. *Carcinogenesis* **16**(12)**:**2893-8.